REMARKS/ARGUMENTS

By the present amendment, claims 21-29 have been cancelled as being directed to non-elected inventions and claims 6 and 15 have been withdrawn as being elected to non-elected species. Applicant respectfully requests that upon allowance of a generic claim the Examiner consider the additional species. The office action dated August 17, 2009 has been carefully considered. It is believed that the following comments represent a complete response to the Examiner's rejections and place the present application in condition for allowance. Reconsideration is respectfully requested.

35 USC §112, first paragraph

The Examiner rejected claims 1-5, 7-14 and 16-20 under 35 USC §112, first paragraph, as being non-enabling for a method to treat a subject having a lysosomal storage disease comprising a method wherein a composition comprising a p97 molecule covalently linked to a protein is actually administered to said subject/patient. Applicant respectfully disagrees for the following reasons.

The Examiner alleges that the application provides no evidence that a subject having a lysosomal storage disease can be treated with a composition comprising a p97-protein conjugate, citing the absence of a reduction to practice of the claimed method. The Examiner appears to be requesting *in vivo* data. Applicant respectfully submits that the *in vitro* data provided in the application enables the present claims.

MPEP 2164.02 states:

> Compliance with the enablement requirement of 35 U.S.C. 112 does not turn on whether a working example is disclosed (MPEP 2164.02). **An applicant need not have actually reduced the invention to practice prior to filing.** In Gould v. Quigg, 822 F.2d 1074, 1078, 3 USPQ 2d 1302, 1304 (Fed. Cir. 1987)

Applicant was the first to demonstrate that p97 is capable of targeting its conjugated partner into the lysosome of a cell (see Examples 1 and 2 of the specification). Applicant respectfully submits that the *in vitro* data disclosed in the application are enabling, as the demonstration of *in vitro* p97 localization to the lysosome and characterization of p97-enzyme conjugates correlates with the *in vivo* effect.

As mentioned above, the present inventors have shown in Examples 1 and 2 of the specification that p97 is capable of targeting its conjugated partner into the lysosome of a cell. Further, p97 has been previously demonstrated to deliver compounds through the blood brain barrier (Jefferies et al. 5,981,194). We also refer to the Declaration under 37 CFR 1.132 by Dr. Wilfred Jefferies dated April 27, 2009 that was filed on April 28, 2009 (hereinafter "the first Jefferies Declaration"). The first Jefferies Declaration shows in paragraphs 8 and 9 that p97 is transcytosed across the blood brain barrier in a model known to correlate with blood brain barrier transcytosis *in vivo*, in paragraph 10

that various p97-N-iduronidase conjugates were made and in paragraph 11 that p97 and iduronidase co-localize in the lysosome of a cell.

Thus, the data show that the fusion of p97 with a lysosomal enzyme is enzymatically active, that the structural integrity of the lysosomal enzyme is maintained, and that the enzyme can be separated from p97 by cleavage by cathepsins that normally reside in the lysosome. Thus, fusions of p97 with lysosomal enzyme should be taken up like p97 and then released via cathepsin activity. In view of the foregoing, Applicant submits that this data provides a clear correlation to the *in vivo* delivery of enzyme via p97 to the lysosome of the cell.

As mentioned in the previous response filed April 28, 2009, lysosomal storage disease is the basis for the traditional treatment of intravenous enzyme replacement therapy and thus it is not necessary to show that lysosomal enzyme therapy itself is effective. The present application is an improved therapy in that it delivers the lysosomal enzyme to the lysosome of the cell. Since lysosomal storage diseases are characterized by a build up of undegraded "storage material" in the lysosome of a cell due to lack of enzyme, we reiterate that it is understood that providing the enzyme not only to the affected tissue but to the lysosomes in the cells of the affected tissue would be an effective therapy. Thus, the examples showing that p97 is capable of delivering its fused partner to the lysosome of the cell is sufficient to enable the present methods and compounds.

In addition, the Examiner alleges at page 5 of the Office Action that since the data presented relates to p97-iduronidase conjugate, Applicants' claimed species, β-hexosaminidase A is not enabled. Applicant respectfully disagrees. The exemplary results from a conjugate with one lysosomal enzyme are sufficient to enable a conjugate with a different lysosomal enzyme. In further support, we also include a second Declaration under 37 CFR 1.132 by Dr. Wilfred Jefferies (hereinafter "the second Jefferies Declaration"), which shows that another lysosomal enzyme, N-acetylglucosaminidase (NAGLU) has been successfully conjugated to p97. Dr. Jefferies also reviews several examples of p97 conjugates in the literature that show its ability to cross the blood brain barrier *in vivo*.

The Examiner also alleges that the presence of the enzyme in the lysosome of a cell *in vitro* is not convincing evidence that a subject administered a composition comprising iduronidase covalently linked to p97 has been treated with a lysosomal disease, especially in the absence of evidence that "said composition is comprised of a linker as claimed instantly". Applicant respectfully disagrees with the Examiner. The Examiner is construing claim 1 to include the presence of a linker but claim 1 merely recites that p97 is covalently linked to the lysosomal enzyme. A covalent linkage between two proteins as recited in claim 1 does not require the presence of a linker. In fact, the presence of a linker is only a specific embodiment, which is found in dependent claim 7. Further, the presence of a linker is to facilitate the structural integrity of the conjugate. The data presented in the first Jefferies Declaration and in the second Jefferies Declaration in Exhibit B show that p97-linker-iduronidase conjugates were prepared, maintained

structural integrity, and released the iduronidase in the presence of cathepsin D. The fact that the fluorescence experiments with p97 or iduronidase showing localization to the lysosome did not include a linker is not significant. A person skilled in the art would consider the linker to be of no consequence to such localization.

The Examiner further alleges that "the delivery of the composition to the target site, clearance rate, degradation, the timing of delivery compared to chronological age, and other physiological factors have not been determined, let alone suggested". Applicant respectfully reiterates that such pharmacodynamic properties are not necessary for enablement and it would be unfair to demand such data as it would require that the Applicant begin clinical trials before submitting a patent application. There are numerous decisions of the Board of Patent Appeals and Interferences that have held that with respect to proteins, such as antibodies for example, *in vitro* data is sufficient to enable claims that cover *in vivo* applications (*Ex parte Bernard* (Appeal no. 2001-2379)). The same issues that the Examiner alleges would exist for the currently claimed conjugate would also exist for an antibody, i.e. whether the antibody would be delivered to the target site, the clearance rate, degradation, timing of delivery compared to chronological age, and other physiological factors and yet the Board of Patent Appeals and Interferences held that the claims in *Ex parte Bernard* were enabled. Applicant respectfully submits that once p97 targeting to the lysosome has been established *in vitro* and structural integrity of the fusion is shown, those skilled in the art would accept that the molecule in question would be a viable drug candidate. In addition, as mentioned in the second Jefferies Declaration, there are examples in the literature that have demonstrated *in vivo* administration of p97-conjugates and subsequent delivery to the brain.

In view of the foregoing, we respectfully request that the rejection to the claims under 35 USC §112, first paragraph, be withdrawn.

The Commissioner is hereby authorized to charge any fee (including any claim fee) which may be required to our Deposit Account No. 02-2095.

In view of the foregoing comments and amendments, we respectfully submit that the application is in order for allowance and early indication of that effect is respectfully requested. Should the Examiner deem it beneficial to discuss the application in greater detail, she is kindly requested to contact the undersigned by telephone at (416) 957-1678 at her convenience.

Respectfully submitted,

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By _____

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